

CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Assistant Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claims 15-17 were objected to as being improper dependent claims. In response, Applicants have amended claim 15 to specify that the integration is into a polymerase II dependent locus.

Claims 1, 5-6, 8-24, 26-27 and 29 were rejected under 35 USC § 112, first paragraph, as being broader than the enabling disclosure. In response, Applicants point out that the “nonhuman vertebrate” has been limited to mice and fish.

The Examiner concedes enablement for mice. At the time of the present invention, persons skilled in the art would have expected that gene knock-down/gene knock-in either randomly or through homologous recombination could be successfully performed in any animal species once it had been shown in mice. Consequently, Applicants respectfully submit that the Examiner should accept enablement for fish as well.

Applicants believe that the limitation in scope provides reasonable assurance that the full scope of the now limited claims should be capable of being practiced by persons having ordinary skill in the art without undue experimentation. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 15-17 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, as noted above, Applicants have amended claim 15 to specify that the integration is into a polymerase II dependent locus.

Claims 1, 5-10, 13-24, 26-27 and 29-30 were rejected under 35 USC § 103(a) as being obvious over Beach et al. ("Beach"), US 2003/0084471, Bronson et al. ("Bronson"), *PNAS*, 93: 9067-9072 (1996), and Soriano et al. ("Soriano"), US 6,461,864.

Claims 1, 5-24, 26-27 and 29-30 were rejected under 35 USC § 103(a) as being obvious over Beach, Bronson, Soriano and Ohkawa et al. ("Ohkawa"), *Hum. Gene. Ther.*, 11: 577-85 (2000).

In response to **both** obviousness rejections, Applicants respectfully submit that neither combination of references makes out a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw both rejections.

As Applicants already pointed out on page 13 of the amendment dated January 26, 2007, Soriano relates to ubiquitous expression of a heterologous gene inserted into the Rosa 26 locus by homologous recombination, wherein the endogenous Rosa 26 promoter derives transgene expression via a splice acceptor sequence. Thus, Soriano does not relate to the use of exogenous promoters, notably exogenous polymerase I, II and III dependent promoters as the present application. Given the fact that Bronson provides for a random transgenesis method which is unspecific as to the site of integration and use of the promoter; and Beach relates to a random integration system and does not mention the polymerase II dependent locus, a person skilled in the art – even if combining the teachings of said three references – would not have arrived at the claimed subject matter. The Examiner has assumed an inherent feature, e.g. that integration in Beach might occur at a polymerase II dependent locus (but there is however no teaching in Beach that the integration should occur at this locus), and has then combined this assumed inherent feature with that of other references to arrive at the claimed subject matter. While the assumption of an inherent feature for the discussion of novelty is appropriate, Applicants respectfully submit that the combination the Examiner proposes is certainly improper in the context of obviousness. It is not possible to arrive at the teaching of Beach as done by the Examiner without improper hindsight. In Applicants' opinion, the particular combination, namely the stable integration into a polymerase II

dependent locus by homologous recombination of an expression vector comprising a short hairpin RNA under control of a polymerase I, II or III dependent promoter, is not rendered obvious by any of the cited references taken alone or in combination. Moreover, the combination of the cited references would not allow the skilled person to predict that the strong expression of shRNA in a transgenic animal is possible with the animal model obtained by the claimed method.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw both obviousness rejections. An early notice that both obviousness rejections have been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
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